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TITLE: Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaska

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14. ABSTRACT The intent of this proposal is to conduct a case-control study of Parkinson's disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 is a developmental period and is complete for study conduct statewide. The specific aspects of the study design were established, detailed protocols were developed, and Institutional Review Board (IRB) approval was obtained. Phase 2, conduct of the case-control study, is now in progress statewide.					
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A. Introduction

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Native people to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides, and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interviews, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 was a developmental period and is complete. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Phase 2, conduct of the case-control study, is now in progress.

B. Body

SCOPE OF WORK - PHASE 1

Task 1: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.

Task 2: Develop methods for identifying matched controls.

Accomplishments:

Approved methods were utilized to identify cases and controls for recruitment at the Alaska Native Medical Center (ANMC) in Anchorage. During the past year, we concurrently ascertained and enrolled cases and controls statewide in 13 different clinics.

Task 3: Develop a preliminary proposal for review by Alaska Native leaders. Subsequent detailed versions of the study protocol will be submitted for review in accordance with protocol.

Accomplishments:

The study protocol, data collection instruments, and informed consents were submitted and approved by all necessary regulatory boards (see Task 7) and the Human Research Protection Office (HRPO) Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) for study conduct. The approved documents are being utilized to recruit, enroll, and collect data from study participants statewide.

Task 4: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager, and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.

Accomplishments:

Dr. Trimble, our local neurologist, has been involved with the project since its inception. April 2007 we hired an Alaska based project manager, Amy Wiita. She remains a key member of the research team. Additionally, Monica Korell, who has been with the project since its inception, continues as the senior study manager. All members of the research team participate in annual human subjects, biologics, and data collection training. The team members maintain regular contact and collegial working relationships with representatives of the 12 tribal health organizations, clinic administrators, and health professionals working with the neurology clinics.

Task 5: Develop study instruments and a detailed protocol.

Accomplishments:

Drafts were completed during year 2. We developed a study protocol and study instruments for collecting detailed life histories with special focus on dietary, residential and occupational exposures. After receiving approval from institutional review boards, the HRPO ORP USAMRMC requested additional changes to the protocol. Those changes were implemented, resubmitted, and approved. Study activities are being conducted under the current approvals.

Task 6: Refining the study protocol and preparing the operations manual.

Accomplishments:

The study protocol was refined and approved for use in Anchorage as well as 9 of 10 regions outside the Anchorage basin. The operations manual was prepared.

Task 7: IRB approval of final protocols.

Accomplishments:

IRB approval to recruit in the ANMC in Anchorage was achieved January 16, 2008, and the study was initiated in Anchorage (see Table 1). In September 2009, we submitted the currently approved protocol and participant materials to all 10 regional tribal boards outside of Anchorage. We continue to meet with tribal boards and local clinic staff in order to describe the study hypotheses and protocol, provide annual updates on study progress, and to answer any questions they might have. Final approval is complete in 9 of the 10 regional boards. The remaining approval is still being negotiated (Table 3).

Table 1. Human Subject Approval Status

Institution	Review Board	Status
Parkinson's Institute	Western IRB	Approved
Alaska Native Medical Center	AK Area IRB	Approved
Pacific Health Research Institute	VA Pacific Islands Health Care System	Approved
University of California San Francisco	UCSF Committee on Human Research	Approved
USAMRMC	Office of Research Protections	Approved

Table 2. Anchorage Service Unit Tribal Health Boards

Institution	Review Board	Status
Alaska Native Medical Center	AK Native Tribal Health Consortium	Approved
Alaska Native Medical Center	SouthCentral Foundation	Approved

Table 3. Regional Tribal Health Boards (regions outside the Anchorage service unit)

Region Served	Review Board	Submission Status	Approval
Kotzebue	Manilaq Association	Complete	Approved
Sitka, Juneau, Klawok	Southeast AK Regional Health Consortium	Complete	Approved
Fairbanks	Tanana Chiefs Council	Complete	Approved
Nome	Norton Sound Health Corporation	Complete	Approved
Bethel	Yukon Kuskokwim Health Corporation	Complete	pending
Kodiak	Kodiak Area Native Association	Complete	Approved
Dillingham	Bristol Bay Area Health Corporation	Complete	Approved
Barrow	Arctic Slope Native Association	Complete	Approved
Ketchikan	Ketchikan Indian Community	Complete	Approved
Metlakatla	Metlakatla Indian Community	Complete	Approved

SCOPE OF WORK - PHASE 2

Phase 2 was initiated in February 2008.

The goals of this phase are:

Task1: Identify approximately 50 cases of PD and 150 age matched participants without PD among the Native population in Alaska. This will be accomplished by working through tribal leaders, local health care providers and local contacts at the IHS to assist with identifying the most efficient and appropriate means of identifying cases and controls. Specifically, we will request assistance with gaining access to the IHS computerized medical record, the IHS hospital discharge data system, and pharmacy databases. These databases will be used to identify individuals with a diagnosis of PD and individuals on PD medications. Potential participants will be contacted by phone and administered a PD screening instrument. Those who agree to participate and who screen positively will be examined by a trained physician who will use standardized instruments for assessing Parkinson's disease (Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, etc.). Participants will be videotaped to allow

expert confirmation of diagnosis. Control participants will be selected from the same population and similarly screened.

Accomplished:

Cases: We established a list of International Classification of Disease (ICD-9) codes related to PD. Patient databases at all clinics where approval has been achieved are periodically searched for these codes. The outputs from the searches are compiled by Dr. Trimble to identify and prioritize suspect cases for study enrollment.

186 cases suspected of having a PD diagnosis have been screened (initial review of medical record to determine study eligibility)

- 21 Enrollment is in progress
- 66 provided informed consent and are enrolled
 - 48 finished all parts of interview
 - 15 evaluations / interviews in progress
 - 3 ineligible
- 10 refusals
- 77 ineligible
- 0 on hold
- 12 more information needed to assess eligibility

Controls: During the past year, we resumed identification and enrollment of matched controls statewide.

273 potential controls screened statewide

- 19 Enrollment in progress
- 139 provided informed consent and are enrolled
 - 105 have finished all parts of interview
 - 30 interview in progress
 - 3 ineligible
 - 1 refused
- 20 refusals
- 29 ineligible
- 66 on hold

Task 2: Draw blood from cases and controls to measure levels of PCBs, organochlorine pesticides and methyl mercury.

Accomplished:

Ongoing training is conducted to ensure the proper collection, shipment, and processing of blood samples. We established a network of clinic phlebotomists to be on-call for study blood draws. After labeling, the blood samples are shipped overnight to the Parkinson's Institute laboratory for processing and storage. To date, samples from 176 subjects have been collected, shipped, and processed.

Task 3: Administer a structured interview to cases and controls to identify information important to the characterization of PCB, organochlorine pesticides and methyl mercury exposure (life time diet, occupation, place of residence, recreational activities) or identifying potential confounders (smoking cigarettes, drinking coffee, alcohol).

Accomplished:

Of the 205 subjects enrolled to date, 153 interviews have been completed, 45 are in-progress, and 6 enrollees were deemed ineligible for analysis, and 1 refused to complete data collection after enrollment.

Task 4. Estimate logistic regression models adjusted for age and other potential confounders to determine the odds of PD among those with high levels of PCB , organochlorine pesticides and methyl mercury exposure, individually and in combination, relative to the odds of PD among those with no or low levels of exposure the toxicants.

Accomplished:

Databases were developed at the Parkinson's Institute, and procedures for data entry and quality control implemented. We held 3 investigator meetings at the Parkinson's Institute to outline sample analyses and final analytic plans to be implemented once data collection is complete.

C. Key Research Accomplishments

- Held bi-monthly, face-to-face meetings with collaborators in AK to discuss study progress, challenges, and potential refinement to methods of case and control ascertainment.
- Case ascertainment, review of potential case medical records by Dr. Trimble, enrollment and data collection continued in Anchorage, Juneau, Sitka, Klawok, Metlakatla, Nome, Kotzebue, Barrow, Dillingham, Ketchikan, Fairbanks, and Kodiak.
- Control enrollment was accelerated statewide in all approved regions.
- Continued in-person presentations and face to face meetings, and paper reporting to tribal health organizations, clinic administrators, and health professionals working with the neurology clinics to give study updates and address concerns and interests unique to each regional clinic. To date we received complete approval from 11 of 12 tribal boards. The 1 remaining, Yukon Kuskokwim health Corporation, gave us approval in principle with specific consent language still being negotiated for recruitment in their region.
- Initiated case adjudication by 2 movement disorders specialists in order to apply study diagnostic criteria for parkinsonism and to verify diagnosis.

D. Reportable Outcomes

We will not have reportable outcomes until all data collection is finished statewide.

E. Conclusions

Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions. Based on study progress to date, we are confident that we will successfully meet our PD ascertainment goal of 50 individuals meeting strict study diagnostic criteria with complete data collection.

F. References

None

G. Appendices

None